

*REMARKS/ARGUMENTS**The Pending Claims*

Claims 1-11 are pending and are directed to a method of growing spermatogonial stem cells.

The Amendments to the Claims

Claim 1 has been amended to recite that the stem cells are cultured for at least 3 to 4 weeks, as supported by the specification at, for example, page 21, lines 25-29, and page 35, line 16, through page 36, line 4. Claim 12 has been canceled. Claims 13-27 have been canceled as drawn to a non-elected invention. No new matter has been added by way of these amendments.

Summary of the Office Action

The Office makes final the restriction requirement and withdraws claims 13-27 from consideration.

The Office rejects claim 12 under (i) 35 U.S.C. § 102(a) or 102(b) as allegedly anticipated by each of Nagano et al. (*Biol. Reprod.*, 68: 2207-2217 (2003); Reference AK); Nagano et al. (*Tissue & Cell*, 30(4): 389-397 (1998); Reference AH); and Nagano et al., (*Proc. Natl. Acad. Sci. USA*, 98(23): 13090-13095 (2001); Reference AJ) (referred to herein as “the Nagano references”).

The Office rejects claims 1-3, 5, 6, and 12 under 35 U.S.C. § 102(b) as allegedly anticipated by Creemers et al. (*Reproduction*, 124: 791-799 (2002)) as evidenced by the material set forth on the embryology website, namely <http://www.embryology.ch/anglais/cgametogen/spermato03.html>.

The Office rejects claims 1-12 under 35 U.S.C. § 103(a) as allegedly unpatentable over Creemers et al. as evidenced by the embryology website and each of (i) Nagano et al. (*Biol. Reprod.*, 68: 2207-2217 (2003); Reference AK); (ii) Wahab-Wahlgren (*Mol. Cell. Endocrin.*, 201: 39-46 (2003)) and Haneji et al. (*J. Endocrin.*, 128: 383-388 (1991)); and (iii) Izadyar et al. (*Biol. Reprod.*, 68: 272-281 (2003)).

Reconsideration of these rejections is hereby requested.

Discussion of the Anticipation Rejections

The Office contends that the Nagano references anticipate the subject matter of claim 12. Claim 12 has been canceled, thereby rendering the rejection moot.

The Office contends that the Creemers reference anticipates the subject matter of claims 1-3, 5, 6, and 12 by disclosing culturing mouse type A spermatogonia in a medium containing LIF, bFGF, and GDNF (e.g., 2, 10, or 25 ng/ml), which also can contain serum. The Office contends that the embryology website, <http://www.embryology.ch/anglais/cgametogen/spermato03.html>, discloses that type A spermatogonia contains stem cells.

The pending claims, as amended, require that the spermatogonial stem cells are cultured for at least 3 to 4 weeks in a medium containing GDNF or an equivalent thereto and LIF. The Creemers reference discloses that the culture period is 7 days at the longest and that the viability of type A spermatogonia decreases to only about 10% after culture for 7 days in medium containing LIF and bFGF (see page 794, first column, third full paragraph, and Figs. 2, 3, and 5). The Creemers reference discloses that the addition of GDNF did not significantly influence the viability of type A spermatogonia (see page 794, first column, third full paragraph).

In that the Creemers reference does not disclose culturing the spermatogonial stem cells for at least 3 to 4 weeks as required by the pending claims, the Creemers reference (alone or in view of the embryology website) cannot be considered to anticipate the inventive method.

For the above-described reasons, Applicants request that the anticipation rejections be withdrawn.

Discussion of the Obviousness Rejections

The Office relies upon the Creemers reference (as evidenced by the embryology website) as described above in reference to the anticipation rejection of claims 1-3, 5, 6, and 12. The Office considers that one of ordinary skill in the art could determine the LIF and

bFGF concentrations recited in dependent claims 7 and 9 by routine optimization. The Office contends that the Nagano, Wahab-Wahlgren, Haneji, and Izadyar references allegedly disclose features of dependent claims 2, 4, and 7-11.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned *Graham* factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited references.

As regards the scope and content of the prior art, the Creemers reference discloses culturing mouse type A spermatogonia in a medium containing LIF, bFGF, and GDNF (e.g., 2, 10, or 25 ng/ml), which also can contain serum. The Nagano reference discloses culturing spermatogonial stem cells with feeder cells. The Wahab-Wahlgren and Haneji references characterize the effect of EGF on spermatogonia proliferation/differentiation. The Izadyar reference discloses culturing bovine type A spermatogonia in differing amounts of serum.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

The present invention, as defined by the pending claims is directed to a method of growing spermatogonial stem cells. The method comprises growing spermatogonial stem cells by culturing the spermatogonial stem cells for at least 3 to 4 weeks using a medium containing GDNF or an equivalent thereto and LIF.

As discussed above, the Creemers reference does not disclose culturing spermatogonial stem cells for at least 3 to 4 weeks as required by the pending claims. The Creemers reference discloses that the culture period is 7 days at the longest and that the viability of type A spermatogonia decreases to only about 10% after culture for 7 days (see page 794, first column, third full paragraph, and Figs. 2, 3, and 5). Based on the disclosure of the Creemers reference, one of ordinary skill in the art would not have any reason to culture spermatogonial stem cells for at least 3 to 4 weeks as required by the pending claims. Indeed, the disclosure of the Creemers reference appears to teach away from using the longer culture periods of the inventive method by disclosing that viability decreases based on the length of the culture period (see page 794, first column, third full paragraph, and Figs. 2, 3, and 5).

The remaining cited references do not disclose culturing spermatogonial stem cells for at least 3 to 4 weeks in a medium containing GDNF or an equivalent thereto and LIF, or provide any reason to modify the method of the Creemers reference to increase the length of the culturing period.

As regards any objective criteria of nonobviousness, Applicants note that the Creemers reference discloses the culture of a mixture of type A spermatogonia of various stages, focuses on the viability of the total mixture of the type A spermatogonia, and demonstrates that the viability of the mixture decreases as a result of culturing for 7 days. In contrast, the inventors focused on the effects of culture conditions on only spermatogonial stem cells (which only make up a small portion of the cells of type A spermatogonia), and interestingly found that when testis cells containing spermatogonial stem cells are cultured in a medium containing GDNF and LIF for at least 3 to 4 weeks, spermatogonia cells other than spermatogonial stem cells may die, but spermatogonial stem cells grow to form stable colonies and can be further passaged for several months (see, e.g., page 21, lines 25-29, and page 35, line 16, through page 36, line 4, of the specification).

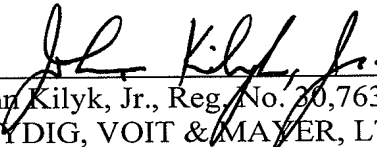
Considering all of the *Graham* factors together, it is clear that the present invention – as defined by the pending claims – would not have been obvious to one of ordinary skill in the art at the relevant time in view of the disclosure of the Creemers reference as evidenced by the embryology website, alone in combination with the disclosures of the Nagano, Wahab-

Wahlgren, Haneji, and Izadyar references. Accordingly, the obviousness rejections should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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